UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/084,139	02/28/2002	Shigekazu Nagata	1110-0307P	7006

2292 7590 01/13/2005

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/084,139	Applicant(s) NAGATA ET AL.	
	Examiner Eileen O'Hara	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1-7 and 10-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8, 9 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-15* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09297,328.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/28/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-15 are pending in the instant application. Claim 15 has been amended as requested by Applicant in the Paper filed Sept. 21, 2004.

Election/Restrictions

2. Applicant's election without traverse of Group II, claims 8, 9 and 15 in the reply filed on Sept. 21, 2004 is acknowledged.

Claims 1-7 and 10-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 8, 9 and 15 are currently under examination.

Specification

3.1 The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Method of Treating Graft versus Host Disease by administration of a Fas antagonist.

3.2 The disclosure is objected to because of the following informalities:

37 C.F.R. §1.821(d) states:

> Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Sequences are disclosed in Figures 1-12 without the required reference to the sequence identifiers (SEQ ID NOS:). Also, the instant specification needs to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. This can be resolved by adding a reference to the Figures or the Brief Description of the Drawings. For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

Applicants are required to amend the specification to comply with 37 C.F.R. §1.821(d).

3.3 The specification needs amending to incorporate standard English syntax and grammar. The specification is replete with sentences which do not have articles (see page 1, lines 16, 20 and 24, for example), improper verb tenses (see page 2, second paragraph, line 1) and so forth. Appropriate action is required.

3.4 The use of the trademarks such as "AFFI-PREP", page 39, line 4, "FILTRON OMEGA CELL:, page 39, line 8, "CELLOFINE", page 57, line 4, "MONO-S", page 5 and so on, have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

3.5 Each letter of the trademarks must be capitalized. See MPEP 608.01 (V) and Appendix 1.

Priority

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) as well as the status of the application in the first sentence of the specification (37 CFR 1.78).

Claim Objections

5. Claim 9 is objected to because of the following informalities: it recites "has ***an*** activity of inhibiting apoptosis", and it should be "has ***the*** activity of inhibiting apoptosis". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6.1 Claims 8, 9 and 15 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using Fas antagonists to treat Graft versus Host Disease (GVHD) that are Fas derived, anti-Fas antibodies or anti-Fas ligand antibodies, does not reasonably provide enablement for using antisense oligonucleotides for the mRNA or the gene of Fas or Fas ligand, or a substance which interacts with the intracellular domain of Fas, or an ICE inhibitor. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In the specification the paragraph bridging pages 20-21 discusses that a Fas antagonist may be an antisense oligonucleotides for the mRNA or the gene of Fas or Fas ligand, or a substance which interacts with the intracellular domain of Fas. Therefore claims 8, 9 and 15 encompass gene therapy or treatment with a substance which interacts with the intracellular domain of Fas. The instant application provides the results of experiments that demonstrate that Fas antagonists that are Fas-Fc fusion and antibody to Fas ligand increase the survival of mice in a GVHD mouse model. However, the claims encompass gene therapy and treatment with a substance which interacts with the intracellular domain of Fas or treatment with an ICE inhibitor, and the specification has not provided the support and guidance necessary to use those methods. There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

The specification and prior art have not provided adequate guidance as to the vectors, promoters, transcriptional elements, and administration methods, for example, which are necessary for gene therapy, and the specification does not provide any working examples. The level of skill in the art of gene therapy is low, and there have been very few successful gene

therapy treatments. Thus, the specification fails to teach the skilled artisan how to use the claimed invention without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to perform gene therapy. Due to the large quantity of experimentation necessary, the lack of direction/guidance presented in the specification regarding same and the absence of working examples, and lack of success in the prior art, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

The state of the art of gene therapy at the time of the invention was low, with no unambiguous therapeutic benefits. Science News Report (Science 269, page 1050, column 2, paragraph 1, lines 6-15) states that while there have been reports of convincing gene transfer and expression, there is little evidence of a therapeutic result in patients or animal models. Anderson (Scientific American, September 1995, pages 124-128) states that *in situ* therapy, is hampered by effective ways for implanting corrected genes into various organs, as the genes are not expressed sufficiently to produce sufficient quantities of protein. Blau et al. (The New England Journal of Medicine, Nov. 2, 1995, pages 1204, column 1-2 bridging sentences and page 1205, column 1-2, bridging paragraph and page 1207, second column) wrote that expression and delivery of the gene desired for treatment were seen as the hurdles yet to be overcome, and that thus far clinical trials have not shown convincingly that gene therapy is effective in treating disease in humans, and the field is still in its infancy.

As for treatment of GVHD with a substance which interacts with the intracellular domain of Fas, or for an ICE inhibitor (ICE is intracellular), there is no disclosure of any substance that would bind to the intracellular domain of Fas and inhibit signaling or inhibit ICE, and even if

and even if such a substance were disclosed, it is not clear that such a substance would be transported across the cell membrane, which would be necessary for activity.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification what substances could bind to the intracellular domain of Fas and inhibit signaling or what substances could inhibit ICE activity. There are no examples of any such substances. Thus, the specification fails to teach the skilled artisan how to treat GVHD with such compounds without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the encompassed method, except for treatment with Fas or anti-Fas or anti-Fas ligand antibodies.

Due to the large quantity of experimentation necessary to determine if the substance which interacts with the intracellular domain of Fas, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

6.2 Claims 8, 9 and 15 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification discloses experiments that

demonstrate that Fas antagonists that are Fas-Fc fusion and antibody to Fas ligand increase the survival of mice in a GVHD mouse model. However, claims 8, 9 and 15 also encompass method of treating GVHD comprising administering a substance which interacts with the intracellular domain of Fas, or inhibits ICE, and the specification has not identified any such substances. Therefore, the specification does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification does not disclose however, a single substance that would bind the intracellular domain of Fas that would inhibit Fas signaling, or inhibit ICE, and so does not meet the written description requirement.

Priority Determination

7. The effective priority date of the instant application is determined to be Oct. 31, 1997, because a translation of the foreign papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8.1 Claims 8, 9 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Palmer et al., U.S. Patent No. 5,776,718.

Claims 8, 9 and 15 encompass a method of treating graft versus host disease comprising administering a Fas antagonist.

In the specification the paragraph bridging pages 20-21 discusses that a Fas antagonist may be an ICE inhibitor, which is involved in the signal transduction of the Fas-mediated apoptosis.

Palmer et al. disclose ICE inhibitors, and teaches that these compounds may be used in the treatment of graft versus host disease (column 30, line 57 to column 31, line 22). Therefore, Palmer et al. anticipates the claims.

8.2 Claims 8, 9 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Du et al., BBRC, Vol. 226, pages 595-600, Sept. 24, 1996.

Claims 8, 9 and 15 encompass a method of treating graft versus host disease comprising administering a Fas antagonist.

Du et al. teach that a hammerhead ribozyme that targets both Fas-ligand and perforin mRNAs, and is thus a Fas antagonist, can be used in a method of treating GVHD. Therefore, Du et al. anticipates the claims.

8.3 Claims 8, 9 and 15 are rejected under 35 U.S.C. 102(b) as being anticiated by Braun et al., J. Exp. Med., Vol. 183, pages 657-661, February 1996.

Braun et al. discloses experiments in a mouse GVHD model in which donor cells from Fas-L deficient mice delayed the onset of GVHD versus compared to donor cells that had functional Fas-L (Figure 4a), and teach that the development of therapeutic strategies aimed at controlling this cytolytic pathway (in addition to perforin, which was also shown to be an important mediator of GVHD) during bone marrow transplantation may be an approach for

decreasing the risk of GVHD (page 660, last paragraph). Therefore, Braun et al. anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8, 9 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palmer et al., U.S. Patent No. 5,776,718, or Du et al., BBRC, Vol. 226, pages 595-600, Sept. 24, 1996, or Braun et al., J. Exp Med., Vol. 183, pages 657-661, February 1996, and further in view of Lynch et al., 5,620,889.

The teachings of Palmer et al., and Du et al. and Braun et al. are discussed above. Lynch et al. teach monoclonal antibodies to Fas, and teach that such antibodies can be used therapeutically to inhibit Fas ligand mediated apoptosis of cells (abstract, column 2, lines 18-52).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to treat GVHD with the antibodies of Lynch et al., since Lynch et al. demonstrated that the anti-Fas antibodies were effective in inhibiting the Fas mediated pathway, and Palmer et al., and Du et al. and Braun et al. teach that the Fas pathway is involved in GVHD. The skilled artisan would be motivated to do so because the antibodies could be made and purified in large quantities, and Lynch et al. demonstrated that the antibodies were effective in inhibiting the Fas pathway.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

EILEEN B. O'HARA
PATENT EXAMINER